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1 IDENTIFICATION OF THE DEVICE AND THE MANUFACTURER

1.1 Device Trade Name

Genius™ Digital Imager and Genius™ Cervical AI

1.2 Legal Manufacturer Address

Hologic, Inc.
250 Campus Drive
Marlborough, MA 01752
USA
1 (800) 442-9892, +1 (508)-263-2900, www.hologic.com

1.3 Manufacturer Single Registration Number (SRN)

US-MF-000001677

1.4 Basic UDI-DI

The basic UDI as referred to in Part C of Annex VI for Genius Digital Imager and Genius Cervical AI is 54200455CYTDIGITALVM.

1.5 Medical Device Reference Codes

GMDN Code: 62575 (Microscope slide digital imaging scanner IVD)
EU Medical Device Nomenclature Code: W02029099 (Cervical Screening Systems)

1.6 Class of Device

Per the in vitro Diagnostic Regulation (IVDR, EU 2017/746) Article 2 and Annex VIII, the Genius Digital Imager and Genius Cervical AI is considered a Class C *in vitro* diagnostic device per Rule 3(h).

1.7 Initial Certificate (CE) Issuance

The initial CE issuance for the Genius Digital Imager and Genius Cervical AI: IVDR 740190.

1.8 European Authorized Representative

Hologic BV
Da Vincilaan 5
1930 Zaventem, Belgium

1.9 European Authorized Representative Single Registration Number (SRN)

SRN: BE-AR-000000127

1.10 Notified Body

BSI Group, The Netherlands B.V.
Say Building

John M. Keynesplein 9
1066 EP Amsterdam
The Netherlands
Notified Body Number: 2797

2 THE INTENDED PURPOSE OF THE DEVICE AND ANY INDICATIONS, CONTRAINDICATIONS AND TARGET POPULATIONS

2.1 Indications for Use/Intended Purpose

The Genius™ Digital Diagnostics System, when used with the Genius Cervical AI algorithm, is indicated for assisting in cervical cancer screening of ThinPrep® Pap test slides, for the presence of atypical cells, cervical neoplasia, including its precursor lesions (Low Grade Squamous Intraepithelial Lesions, High Grade Squamous Intraepithelial Lesions), and carcinoma, as well as all other cytological categories, including adenocarcinoma, as defined *by The Bethesda System for Reporting Cervical Cytology.*

The Genius Digital Diagnostics System can also be used with ThinPrep® non-gynecological microscope slides and ThinPrep® UroCyte® microscope slides to provide a digital image of the whole cell spot for screening.

The Genius Digital Diagnostics System includes the Genius™ Digital Imager, the Genius™ Image Management Server (IMS), and the Genius™ Review Station. The system is for the creation and viewing of digital images of scanned ThinPrep® glass slides that would otherwise be appropriate for manual visualization by conventional light microscopy. It is the responsibility of a qualified pathologist to employ appropriate procedures and safeguards to assure the validity of the interpretation of images obtained using this system.

For professional use.

2.2 Target / Testing Population

Gynecological specimens from women during routine screening and patients with a recent previous cervical abnormality.

Non-gynecological specimens and urine specimens may be acquired from any patient population.

2.3 Contraindications

There are no known contra-indications for use.

3 DEVICE DESCRIPTION

3.1 Description of the Device

The Genius Digital Imager, comprised of the Genius Digital Imager (Scanner), Genius Digital Imager Computer and the Imager Software Subsystem, is a component of the Genius Digital Diagnostics System. The Genius Digital Imager is intended to produce full resolution images of ThinPrep processed slides for use by the Genius Cervical AI algorithm for cervical cancer screening

and prepares digital images for storage. It can be used without the Genius Cervical AI algorithm for other sample types for primary diagnosis.

ThinPrep processed microscope slides are stained, cover slipped and loaded into a slide carrier which is placed into the Genius Digital Imager. The Genius Digital Imager has a touch screen for the operator to interact with the system via a graphic menu driven interface. There is a slide ID reader in the Genius Digital Imager that scans the slide's accession ID and then locates the position of the cell spot on the slide. The digital imager scans the entire cell spot to create a high-resolution digital image. The Genius Cervical AI algorithm identifies the most clinically relevant objects and presents the images to the cytotechnologist (CT) for review as a gallery of images. Once the slide is imaged, slide IDs and images are transmitted to the Image Management Server, the slide is then returned to the slide carrier and the Digital Imager scans the next slide.

The Genius Digital Imager is comprised of:

- Genius Digital Imager (scanner) that contains the slide handling robotics, digital camera and other hardware needed to capture whole slide images (WSIs).
- Genius Digital Imager Computer. Loaded onto the Computer is the following (referred to as the Imager Software Subsystem):
    - Software that controls the Genius Digital Imager mechanical functions;
    - Software that acquires the digital image and merges multiple layers into a single, entirely focused image.

Also loaded onto the Imager computer is the Genius Cervical AI algorithm that identifies the most clinically relevant OOIs from the merged image to create a gallery of objects for display on the Review Station. This is a separate Software Subsystem.

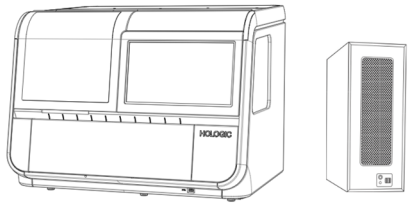
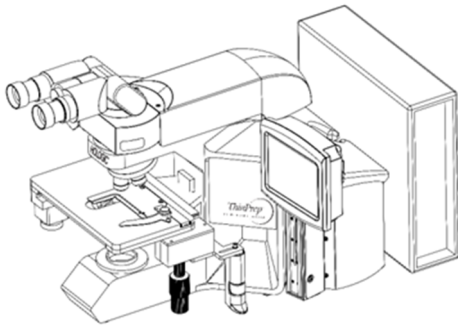
The Genius Cervical AI algorithm is hosted on the Genius Digital Imager Computer and is not stand-alone software. It is separated into its own software subsystem based on its intended use: to use ThinPrep Pap Test slide images produced by the Genius Digital Imager to identify OOIs for presentation to cytotechnologists and pathologists for assisting in cervical cancer screening.

3.2 Previous Generation(s) or Variants

The Genius Digital Diagnostics System is a successor to the ThinPrep Imaging System family that includes the ThinPrep Imaging System (TIS), review scopes, and the Integrated Imager (I2). The Genius Digital Diagnostics System is similar to the ThinPrep Integrated Imager and ThinPrep Imaging System. A comparison of the devices is shown below.

Table 1. Comparison Table of Genius Digital Imager & Genius Cervical AI, ThinPrep Integrated Imager, and ThinPrep Imaging System

Item	Genius Digital Imager and Genius Cervical AI	ThinPrep Integrated Imager (I2)	ThinPrep Imaging System (TIS)
Intended purpose	The Genius Digital Diagnostics System, when used with the Genius Cervical AI algorithm, is indicated for assisting in cervical cancer screening of ThinPrep Pap test slides, for the presence of atypical cells, cervical neoplasia, including its precursor lesions (Low Grade Squamous Intraepithelial Lesions, High Grade Squamous Intraepithelial Lesions), and carcinoma, as well as all other cytological categories, including adenocarcinoma, as defined by *The Bethesda System for Reporting Cervical Cytology*[1]. The Genius Digital Diagnostics System can also be used with ThinPrep non-gynecological microscope slides and ThinPrep UroCyte microscope slides to provide a digital image of the whole cell spot for screening. The Genius Digital Diagnostics System includes the Genius Digital Imager, the Genius Image Management Server (IMS), and the Genius Review Station. The system is for the creation and viewing of digital images of scanned ThinPrep glass slides that would otherwise be	The ThinPrep Integrated Imager is a semi-automated device that uses computer imaging technology to assist in primary cervical cancer screening of ThinPrep Pap Test slides for the presence of atypical cells, cervical neoplasia, including its precursor lesions (Low Grade Squamous Intraepithelial Lesions, High Grade Squamous Intraepithelial Lesions), and carcinoma as well as all other cytologic criteria as defined by *The Bethesda System for Reporting Cervical Cytology*[1]. *For professional use.*	Same as ThinPrep Integrated Imager

Item	Genius Digital Imager and Genius Cervical AI	ThinPrep Integrated Imager (I2)	ThinPrep Imaging System (TIS)
	appropriate for manual visualization by conventional light microscopy. It is the responsibility of a qualified pathologist to employ appropriate procedures and safeguards to assure the validity of the interpretation of images obtained using this system.		
Components of System	The Genius Digital Diagnostics System includes the Genius Digital Imager, the Genius Image Management Server (IMS), and the Genius Review Station. The Genius Digital Diagnostics Imager includes the slide handling system, slide carrier deck, scanning and imaging modules, and electronics and cabling.	I2 consists of a microscope with controller and a computer. Microscope– a microscope with automated stage, hand controls and adjustable touch screen user interface. Controller controls the electromechanical and imaging subsystems. Computer: houses imaging software and stores image data.	TIS consists of Imaging station with Server, Review Scope Manual+ (RSMP), and computer. Imaging Station- images slides in batch and images are stored on the Server. Controller controls the electromechanical and imaging subsystems. Computer: stores image data. Microscope– a microscope with automated stage, hand controls and adjustable touch screen user interface
Image of Device			
Screening Algorithm	Genius Cervical AI algorithm identifies a gallery of the most clinically objects to use for diagnostic purposes. The algorithm	Identifies 22 FOV. Abnormal objects in any FOV triggers full slide review of the ThinPrep microscope slide.	Same as ThinPrep Integrated Imager

Item	Genius Digital Imager and Genius Cervical AI	ThinPrep Integrated Imager (I2)	ThinPrep Imaging System (TIS)
	provides an approximate cell count and identifies microorganisms		

3.3 Accessories

3.4 Accessories for use with the Genius Digital Imager and Genius Cervical AI include the Genius Digital Diagnostics Accessory Kit. Other devices intended to be used in combination with the device

The Genius Digital Imager and Genius Cervical AI are a part of the Genius Digital Diagnostics System which includes the Genius Digital Imager, the Genius Image Management Server (IMS), and the Genius Review Station.

4 RESIDUAL RISKS AND ANY UNDESIRABLE EFFECTS, WARNINGS AND PRECAUTIONS

4.1 Residual Risks and Undesirable Effects

The clinical benefit of the Genius Digital Diagnostics System with Genius Cervical AI is that it assists in cervical cancer screening of ThinPrep Pap Test slides by increasing efficiency of diagnostic screening without compromising clinical diagnostic efficacy. Additionally, the Genius Digital Diagnostics System can be used to provide a digital image of a whole ThinPrep non-gynecological slide for screening. The clinically relevant risks related to *in vitro* diagnostic devices are those risks associated with inaccurate results. In this case, inaccurate results could be associated with an incorrectly imaged slide. Other residual risks include those related to basic safety, including electrical and mechanical risks. All risks have been reduced as far as possible with respect to the benefit-risk ratio and are acceptable when weighed against the benefits. The Genius Digital Diagnostics System IFU and User Manual contains correct information for safety and disclosure of all residual risks.

4.2 Warnings, Precautions and Limitations

4.2.1 Warnings

- For *In Vitro* Diagnostic Use
- The Digital Imager generates, uses, and can radiate radio frequency energy and may cause interference to radio communications.
- Glass. The Digital Imager uses microscope slides, which have sharp edges. In addition, the slides may be broken in their storage packaging or on the instrument. Use caution when handling glass slides and when cleaning the instrument.
- Service Installation Only. The system must be installed by trained Hologic personnel only.

4.2.2 Precautions

- Portable RF communications equipment (including peripherals such as antenna cables and external antennas) should be used no closer than 30 cm (12 inches) to any part of the Digital Imager, including cables specified by the manufacturer. Otherwise, degradation of the performance of this equipment could result.
- Care should be taken to assure that slides are correctly oriented in the Digital Imager slide carrier to prevent rejection by the system.
- The Digital Imager should be placed on a flat, sturdy surface away from any vibrating machinery to assure proper operation.

4.2.3 Limitations

- Only personnel who have been appropriately trained should operate the Genius Digital Imager or Review Station.
- The Genius Cervical AI algorithm is only indicated for use with the ThinPrep Pap test.
- The laboratory Technical Supervisor should establish individual workload limits for personnel using the Genius Digital Diagnostics System.
- ThinPrep microscope slides appropriate for the sample type must be used.
- Slides must be stained using the ThinPrep Stain according to the applicable ThinPrep® Imaging System slide staining protocol.
- Slides should be clean and free of debris before being placed on the system.
- The slide coverslip should be dry and located correctly.
- Slides that are broken or poorly coverslipped should not be used.
- Slides used with the Genius Digital Imager must contain properly formatted accession number identification information as described in the operator's manual.
- The performance of the Genius Digital Diagnostics System using slides prepared from reprocessed sample vials has not been evaluated.
- The monitor and graphics card for the Review Station are those supplied by Hologic specifically for the Genius Digital Diagnostics System. They are required for proper performance of the system and cannot be substituted.

4.3 Quantitative Data

4.3.1 Recall/FSCA/FSN Data

There was one field action during the period of November 01, 2020 to June 30, 2021. One Field Action was initiated to address correction of four units installed at customer locations in Europe for the Digital Imager due to slide stages that did not move freely and failed testing. Slide stages were proactively replaced at the customer sites for these four units. This was not considered to be a recall in the EU because the action taken by the manufacturer was not initiated to reduce a risk of death or serious deterioration in the state of health associated with the use of the medical device that is already placed on the market. There is no impact to safety, efficacy, or the quality of the medical device. The impact to the customer would be noticing an audible noise or the increase in stage move errors. Due to the closed loop control of the system, there would be no impact to image quality or the ability to make a diagnosis.

5 SUMMARY OF PERFORMANCE EVALUATION AND RELEVANT INFORMATION ON PMPF

Analytical and clinical studies were performed by Hologic to evaluate the performance of the Genius Digital Diagnostic System. As the Genius Digital Diagnostic System does not measure an analyte, scientific validity was established by a clinical study, recommendations from clinical practice guidelines, and literature citing liquid-based cytology (LBC) specimens with the use of image assisted screening systems are generally accepted.

Analytical Studies

Objects of Interest (OOI) Study

A laboratory study was conducted to demonstrate that the Genius Cervical AI algorithm accurately selects OOIs using digital images created by the Genius Digital Imager. An OOI is a cell or cluster of cells on a slide preparation that most likely contains clinically relevant information for diagnostic

purposes. The study compared OOIs selected by the Genius Cervical AI algorithm to the same samples imaged and reviewed by CTs using the ThinPrep Imaging System (TIS-assisted review). The study evaluated the performance of the Genius Cervical AI algorithm to present images suitable for diagnosing abnormal cervical cases, for detecting the presence of common infectious organisms in a case, and for detecting the presence of endocervical component (ECC) in a normal case. The study also measured reproducibility of the Genius Digital Diagnostics System.

In the study, 259 ThinPrep slides were enrolled, made from individual residual ThinPrep Pap test specimens, covering the full range of abnormal diagnostic categories as defined in *The Bethesda System for Reporting Cervical Cytology*. The slides were imaged once on the ThinPrep Imaging System, and the same slides were imaged three times on three different Genius Digital Imagers. Slides were reviewed by CTs using the ThinPrep Imaging System (TIS-assisted review), and, after a washout period, the same CTs reviewed the nine runs of that same case on the Genius Digital Diagnostics System. In each review on the Genius Digital Diagnostics System, the CT recorded what the CT observed in every tile in the gallery for the case on the Review Station. The CT reviews were conducted per standard laboratory procedure, recording the diagnostic result, the presences or absence of endocervical component (ECC) and the presence of any infectious organisms, such as trichomonas, candida, coccobacillus, for the TIS-assisted review. The accuracy and reproducibility of the Genius Cervical AI algorithm were measured by comparison to the TIS-assisted diagnoses. The average and standard deviation across runs leading to the same diagnosis or higher was the metric used.

The highest OOI category for any case across the nine runs of the case on the Genius Digital Diagnostics System was compared to the diagnostic category for the same slide in the TIS-assisted review. The table below shows the relationship between the Genius Digital Diagnostic System results and the TIS-assisted results.

Table 2. TIS-assisted Results vs. Genius Digital Diagnostic System OOIs

		TIS								
		UNSAT	NILM	ASCUS	LSIL	ASC-H	AGUS	HSIL	CANCER	Total
OOI	NILM	2	83	4	0	0	2	0	0	91
	ASCUS	0	10	6	3	1	0	0	0	20
	LSIL	0	0	5	27	0	0	1	0	33
	ASC-H	0	1	5	11	2	0	7	0	26
	AGUS	0	2	0	0	0	5	1	1	9
	HSIL	0	0	2	2	2	1	49	5	61
	CANCER	0	0	0	0	1	1	6	9	17
		2	96	22	43	6	9	64	15	

The study showed an average of 6.8 OOIs that match or exceed the TIS result for abnormal slides. The standard deviation was 1.3. These results demonstrate that the Genius Digital Diagnostic System accurately selects OOIs that indicate abnormal slide results matching or exceeding TIS-assisted review. And the results are repeatable across multiple instruments and multiple runs.

Endocervical component (ECC) presence is noted during slide review to confirm adequate cellular sampling. ECC consists of either endocervical or squamous metaplastic cells. Because the Genius Cervical AI algorithm prioritizes the presentation of abnormal cells when they are present, ECC

detection was assessed in this study on the subset of slides deemed normal (NILM) by TIS-assisted review. The table below shows the relationship of ECC presence on TIS-assisted versus OOI gallery review using the Genius Digital Diagnostics System. In each case, the "+" or "-" corresponds to ECC present or absent, respectively. The count of slides in each category is shown in the table.

Table 3. ECC Detection on Normal Cases: Agreement between TIS-assisted Review and OOI Study Results

ECC		TIS	
		-	+
OOI	-	4	2
	+	31	59

Agreement Rates	**PPA**	97%	(89%, 99%)
	NPA	11%	(5%, 26%)
Detection Rates	**TIS**	64%	(54%, 72%)
	OOI	94%	(89%, 99%)
	(Diff)	-30%	(-40%, -20%)

The positive and negative percent agreement (PPA and NPA) were calculated with reference to the TIS-assisted result. In addition, the detection rates and difference have also been provided. Confidence intervals for the proportions are calculated using the Newcombe score method and account for correlation between the matched pairs. The ECC detection rate for OOI review was 94%, compared to 64% for TIS-assisted review. There were 31 NILM slides for which ECC was marked as present in the OOI gallery but not noted in TIS-assisted review. Upon further inspection of those cases, the ECC consisted of rare squamous metaplastic cells, which were not noted during the TIS-assisted review.

The presence of infectious organisms is noted as part of slide review to help in the clinical assessment of the case. In this study, slides were enrolled that included three classes of organism: Trichomonas, Candida, and Coccobacilli. The tables below compare the detection of each organism on TIS-assisted review and review of OOIs in the gallery of a Genius Digital Diagnostic Review Station. For each table, the positive and negative agreement rates with reference to the TIS-assisted result are provided. The overall detection rate for each organism and the difference in detection rates (TIS – OOI) are also included.

Table 4. Trichomonas Detection: Agreement between TIS-assisted Review and OOI Study Results

TRICH		TIS	
		-	+
OOI	-	246	1
	+	2	8
Agreement Rates	**PPA**	89%	(57%, 98%)
	NPA	99%	(97%, 100%)
Detection Rates	**TIS**	3.5%	(1.9%, 6.5%)
	OOI	3.9%	(2.1%, 7.0%)
	(Diff)	-0.4%	(-2.5%, 1.6%)

The detection rate for Trichomonas for the Genius Digital Diagnostics System was 3.9%, compared to 3.5% for TIS-assisted review.

Table 5. Candida Detection: Agreement between TIS-assisted Review and OOI Study Results

CAND		TIS	
		-	+
OOI	-	232	5
	+	3	17
Agreement Rates	**PPA**	77%	(57%, 90%)
	NPA	99%	(96%, 100%)
Detection Rates	**TIS**	8.6%	(5.7%, 12.6%)
	OOI	7.8%	(5.1%, 11.7%)
	(Diff)	0.8%	(-1.8%, 3.4%)

The detection rate for Candida for the Genius Digital Diagnostics System was 7.8%, compared to 8.6% for TIS-assisted review.

Table 6. Coccobacilli Detection: Agreement between TIS-assisted Review and OOI Study Results

COCCO		TIS	
		-	+
OOI	-	203	5
	+	21	28
Agreement Rates	**PPA**	85%	(69%, 93%)
	NPA	91%	(86%, 94%)
Detection Rates	**TIS**	12.8%	(9.3%, 17.5%)
	OOI	19.1%	(14.7%, 24.3%)
	(Diff)	-6.2%	(-10.3%, -2.3%)

The detection rate for Coccobacilli for the Genius Digital Diagnostics System was 19.1%, compared to 12.8% for TIS-assisted review. Further inspection of these cases indicated that bacteria were indeed present in moderate quantities on some cells. In this study, the CTs were required to mark the type of each OOI presented, so Coccobacilli would be noted if any normal cells with bacteria overlaid were presented in the gallery. During a TIS-assisted review, and in clinical practice, bacterial infection is typically noted only when it is considered of possible clinical significance (so-called "clue" cells or a large number of infected cells). The difference in detection rates in the study is due to this difference in counting methodology and would not necessarily be reflected in clinical practice.

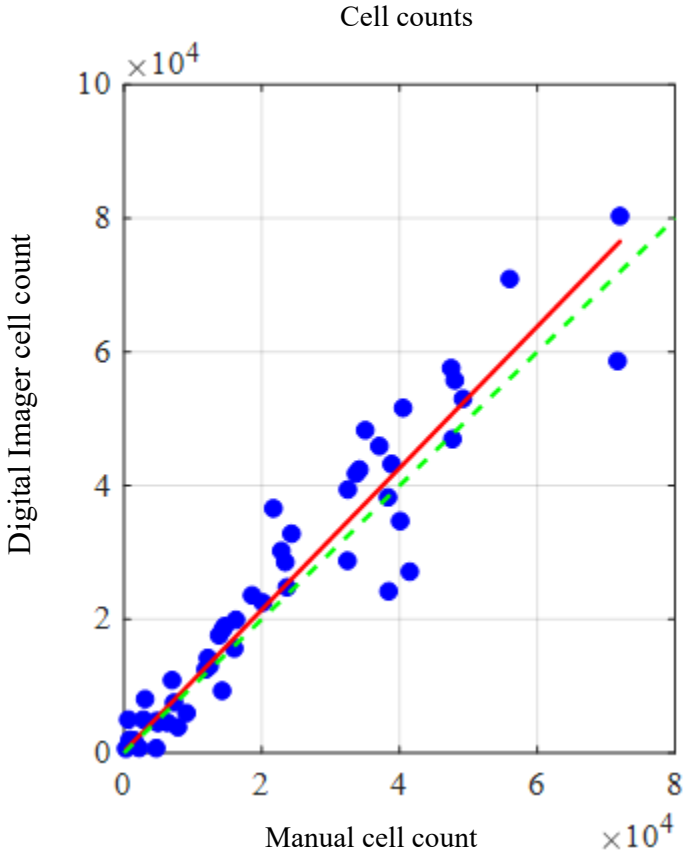
Overall, the presentation of infectious organisms by the algorithm is equivalent or higher than with TIS-assisted review.

Cell Count Study

The objective of this validation test protocol is to measure the accuracy and reproducibility of the cell count metric. ThinPrep Pap test patient sample slides were prepared on a ThinPrep processor, stained and coverslipped. The same slides were imaged on three Genius Digital Imagers. To obtain the manual cell count for the slides in the study, a CT viewed the whole slide image presented on the Genius Review Station, counted the cells presented in a portion of the cell spot image, and estimated the total number of cells based on the portion, similar to the normal process for counting cells on slides viewed on a microscope. The cell counts derived by the Genius Cervical AI algorithm in the Genius Digital Diagnostics system were compared to the manual cell count estimate.

A total of 50 slides, including at least 8 slides with counts near the clinically critical threshold of 5000 cells, were enrolled in the study. The slides covered a range of cellularity typical of a clinical environment. Figure 1 compares the cell counts between the Genius Cervical AI algorithm (the Digital Imager cell count) and a manual cell count method for each slide.

Figure 1. Deming Regression, Cell Count: Digital Imager vs. Manual



The study calculated the average cell count generated by the Genius Cervical AI algorithm for each case across the runs on each of the three Digital Imagers in the study. The intra-instrument %CV in the study was 0.6%. The inter-instrument %CV in the study was 2.7%. The study also estimated the systematic bias of the cell count generated by the Genius Cervical AI algorithm as compared to the manual count, at a count of 5000 cells, the clinical threshold for diagnosis. In the Bethesda System[1], specimens with fewer than 5000 cells are considered unsatisfactory for screening. The count bias in the study was 528, with a 95% CI of -323 to 1379. The results of the study demonstrate that the cell counts generated by the Genius Cervical AI algorithm are comparable to a manual cell count performed by a cytotechnologist.

Clinical Performance

Genius Digital Diagnostics System compared to Manual Review (Genius Cervical AI Clinical Study)

A multi-center study was performed at four (4) sites within the United States. The objective of the study was to show that routine screening of ThinPrep Pap Test slides prepared on the ThinPrep® 2000 System, the ThinPrep® 5000 processor, or the ThinPrep® Genesis™ processor using the Genius Digital Diagnostics System with Genius Cervical AI is non-inferior at the ASCUS+ threshold for all categories used for cytologic diagnosis (specimen adequacy and descriptive diagnosis) as defined by the Bethesda System criteria. The study approach allowed for a comparison of the cytologic interpretation (descriptive diagnosis and specimen adequacy) from a single ThinPrep-prepared slide (of known diagnosis), screened first using manual review and then screened with the assistance of the

Genius Digital Diagnostics System. The adjudicated diagnosis for each case was used as a reference standard for truth to evaluate the results of the study.

Slides utilized in this study were processed on the ThinPrep® processors. All cases were reviewed independently. Each case in the study was screened using standard laboratory cervical cytology practices (manual review), the ThinPrep Imaging System ("TIS" review), pathologist adjudication consensus ("ADJ" review), and finally with the Genius Digital Diagnostics System. A minimum 14-day washout period occurred between each review phase. The slides were randomized prior to case review in each review phase. Cytological diagnoses and specimen adequacy were determined in accordance with the Bethesda System criteria. Study slides prepared from a previous study were used, and additional slides were prepared specifically for this study.

The study results are presented in **Table 7**. In all abnormal categories, the sensitivity and specificity for the Genius Digital Diagnostics System were non-inferior to that of manual review. Superiority for the Genius Digital Diagnostics System as compared to manual review was also evident at the LSIL+, ASC-H+, and HSIL+ diagnostic thresholds for sensitivity.

Table 7. Adjudicated Review vs. Manual Review and Genius Digital Diagnostics System Review, Descriptive Diagnosis Summary (All Cases)

	Sensitivity %			Specificity %		
Diagnostic Threshold	**Manual (95% CI)**	**Genius (95% CI)**	**Difference (95% CI)**	**Manual (95% CI)**	**Genius (95% CI)**	**Difference (95% CI)**
ASCUS+	76.8 (75.8, 77.6%)	76.3 (75.1, 77.6)	0.50 (-0.87, 1.87)	93.0 (92.2, 93.7)	90.1 (89.1, 91.2)	2.83 (1.76, 3.89)
LSIL+	78.8 (77.8, 79.9)	80.9 (79.2, 82.6)	-2.04 (-3.39, -0.69)	95.3 (95.1, 95.5)	91.9 (91.2, 92.6)	3.38 (2.74, 4.03)
ASC-H+	79.1 (77.5, 80.6)	83.7 (82.6, 84.8)	-4.58 (-6.51, -2.65)	96.0 (95.7, 96.3)	92.3 (91.7, 92.8)	3.73 (3.06, 4.41)
HSIL+	72.7 (70.8, 74.5)	78.4 (76.2, 80.6)	-5.69 (-8.51, -2.88)	97.4 (97.1, 97.7)	94.7 (94.0, 95.4)	2.69 (2.04, 3.35)

There was a decrease in false negative HSIL+ diagnoses for the Genius Digital Diagnostic System as compared to manual review. The agreement of HSIL+ diagnoses for manual review with adjudicated review is 72.7%, or a false negative rate of 27.3%. The agreement of HSIL+ cases on the Genius Digital Diagnostics System with adjudicated review is 78.4%, or a false negative rate of 21.6%. This represents a 20.9% reduction in false negative diagnoses for HSIL+.

The study also compared the performance of the Genius Digital Diagnostic System with ThinPrep slides reviewed on the ThinPrep Imaging System (TIS). The results for the Genius Digital Diagnostics System versus TIS review are presented in **Table 8**.

Table 8. Adjudicated Review vs. TIS Review and Genius Digital Diagnostics System Review (Genius), Descriptive Diagnosis Summary (All Cases)

	Sensitivity %			Specificity %		
Diagnostic Threshold	**TIS (95% CI)**	**Genius (95% CI)**	**Difference (95% CI)**	**TIS (95% CI)**	**Genius (95% CI)**	**Difference (95% CI)**
ASCUS+	76.1 (75.0, 77.2%)	76.4 (75.1, 77.6)	-0.24 (-1.18, 0.69)	91.9 (91.2, 92.5)	90.1 (89.1, 91.2)	1.77 (0.83, 2.71)
LSIL+	80.9 (79.7, 82.0)	80.9 (79.2, 82.6)	-0.05 (-1.67, 1.57)	94.2 (93.7, 94.6)	91.9 (91.2, 92.6)	2.27 (1.74, 2.80)
ASC-H+	82.2 (80.8, 83.6)	83.8 (82.8, 84.9)	-1.63 (-3.46, 0.20)	95.0 (94.7, 95.4)	92.3 (91.7, 92.8)	2.75 (2.18, 3.32)
HSIL+	76.9 (74.9, 78.9)	78.5 (76.3, 80.7)	-1.62 (-4.57, 1.33)	96.9 (96.6, 97.1)	94.7 (94.0, 95.4)	2.17 (1.56, 2.79)

As part of the clinical study, the amount of time each CT spent reviewing each case was recorded. The median amount of time per case as well as the minimum time and the maximum time are shown in **Table 9**. In the study, the review time started when the CT clicked on the accession ID until the CT clicked the Complete Review button.

Table 9. CT Review Rates, Time per Case Genius Cervical AI Clinical Study

Site	Reviewer	Median Review Time per Case (minutes:seconds)	Minimum Review Time per Case (minutes:seconds)	Maximum Review Time per Case (hours:minutes:seconds)
Site 1	CT-1	01:59	00:37	10:27
	CT-2	01:03	00:12	42:57
	CT-3	00:46	00:06	27:18
Site 2	CT-1	01:14	00:15	1:10:36
	CT-2	01:46	00:18	29:28
	CT-3	01:39	00:06	32:15
Site 3	CT-1	00:28	00:07	26:25
	CT-2	01:28	00:22	14:55
	CT-3	01:32	00:24	13:31
Site 4	CT-1	01:25	00:20	16:09
	CT-2	01:58	00:29	10:41
	CT-3	01:15	00:32	26:38
Combined		**01:20**	00:06	1:10:36

The sensitivity and specificity of the Genius Digital Diagnostics System for review of slides processed on ThinPrep systems are non-inferior to the sensitivity and specificity of the manual review of the same slides. The sensitivity of the Genius Digital Diagnostics System is superior to the sensitivity of the manual review for the detection of abnormal cells at the LSIL+, ASC-H+, and HSIL+ diagnostic thresholds.

Non-Gynecological Specimen Study

A laboratory study was conducted to demonstrate that the Genius Digital Diagnostics System presents images of non-gynecological cases for slides that would otherwise be appropriate for manual visualization by conventional light microscopy. The study compared results from cases reviewed by a CT using the Genius Digital Diagnostics System to the results of CT review of the same case slides on a microscope (manual review).

Four hundred (400) ThinPrep slides, including a range of non-gynecological specimen types, were enrolled in the study. The study included the following types of specimens: anal Pap, fluids, FNA, respiratory/mucoid, and urine. The specimens were a mix of normal, abnormal, and non-diagnostic cases, according to their donor lab results. The slides were evaluated using a manual microscope as a control. The slides were imaged on a Genius Digital Imager. After a two-week washout period to minimize recognition bias, the case images were evaluated using the Genius Review Station. **Table 10** provides the overall results of the diagnostic screening of the specimens.

Table 10. Matched-Pair Diagnostics Categories, Non-Gynecological Specimens

		Manual		
		Abnormal	**Normal**	**Non-Diagnostic**
Genius	**Abnormal**	147	23	0
	Normal	11	196	8
	Non-Diagnostic	0	0	14

Further analysis of the study data was performed to compare the diagnoses from the Genius case review versus the manual review of the glass slides for slides where a diagnosis was possible. The results are presented in **Table 11**.

Table 11. Proportions of Diagnoses of Abnormal Cases, Non-Gynecological Specimens

	Proportion	**95% confidence interval**
Manual Review	0.419	[0.370 , 0.470]
Genius Digital Review	0.451	[0.401 , 0.501]
Difference, Genius - Manual	0.032	[-0.004 , 0.062]

The study data show that the proportions of abnormal cases in a mix of non-gynecological specimens are equivalent when evaluated with the Genius Digital Diagnostics System and evaluated with manual review. Therefore, non-gynecological cytology specimens may be reliably reviewed for diagnostic evaluation using the Genius Digital Diagnostics System.

Literature Search of Published Data

As the Genius Digital Diagnostic System does not measure an analyte, scientific validity was established by a clinical study, recommendations from clinical practice guidelines, and literature citing LBC specimens with the use of image assisted screening systems are generally accepted. A literature search was conducted from 01 January 2016 through 23 July 2021 to identify published literature. The

literature search protocol was designed to collect pertinent data regarding the state of the art, scientific validity, analytical performance, and clinical performance data for the Genius Digital Diagnostic System. Twelve articles were found to support clinical performance, state of the art, or scientific validity. These articles are described in Table 12.

Table 12: Literature supporting Clinical Performance, State of the Art, and Scientific Validity

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The clinical performance claims for the Genius Digital Diagnostics System is supported by data on 2, 395 slides from a Hologic-sponsored clinical study.
Taken together, the clinical evidence demonstrates the Genius Digital Imager and Genius Cervical AI meets its intended use. No additional PMPF studies are required beyond routine post market surveillance activities.

6 THE METROLOGICAL TRACEABILITY OF ASSIGNED VALUES

The Genius Digital Diagnostic System does not have metrological specifications as it does not have a measuring function or use calibrators or controls.

7 SUGGESTED PROFILE AND TRAINING FOR USERS

The user-specific limitations in the IFU (instructions for use) for the Genius Digital Diagnostic System state:

- Only personnel who have been appropriately trained should operate the Genius Digital Imager.
- For professional use.

8 STANDARDS FOR DEMONSTRATING CONFORMITY

Standard	Year	Title
EN ISO 14971	2019	Medical Devices – Application of risk management to medical devices
EN ISO 13485	2016	Medical Devices – Quality management systems-requirements for regulatory purposes
EN 60601-1-2	2014	Medical electrical equipment - Part 1-2: General requirements for basic safety and essential performance - Collateral Standard: Electromagnetic disturbances - Requirements and tests
EN 61010-1	2010	Safety requirements for electrical equipment for measurements, control and laboratory use – Part 1: General Requirements
EN 61010-2-101	2015	Safety requirements for electrical equipment for measurement, control and laboratory use – Part 2-101: Particular requirements for IVD medical equipment.
IEC 62304	2015	Medical Device Software – Software life cycle processes
EN ISO 18113-1	2011	In vitro diagnostic medical devices – Information supplied by the manufacturing (labelling) Part 1: Terms, definitions and general requirements
EN ISO 18113-3	2011	In vitro diagnostic medical devices – Information supplied by the manufacturing (labelling) Part 3: In vitro instruments for professional use.
EN 62366-1	2015	Medical Devices – Application of usability engineering to medical devices
EN ISO 15223-1	2016	Medical devices - Symbols to be used with medical device labels, labelling and information to be supplied - Part 1: General requirements
EN 61326-1	2013	Electrical equipment for measurement, control and laboratory use - EMC requirements - Part 1: General requirements
EN 61326-2-6	2013	Electrical equipment for measurement, control and laboratory use – EMC requirements – Part 2-6: Particular requirements – In vitro diagnostic (IVD) medical equipment
ASTM D4169-16	2016	Standard Practice for Performance Testing of Shipping Containers and Systems
EN 13612	2003	Performance evaluation of IVD medical devices.
ISO 20916	2019	In vitro diagnostic medical devices – Clinical performance studies using specimens from human subjects – Good study practice

9 REFERENCES

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10 REVISION HISTORY

Document Revision	Date	Description
001	16 SEP 2021	Initial Release
002	22 NOV 2021	Replaced graphics of tables and figure with editable tables and figure with editable labels to support translation activities Deleted the asterisk from Table 9 Reformat bibliography entries in the Literature Search section